

WHAT IS CLAIMED IS:

1. A method for identifying a compound to be
5 tested for an ability to modulate an oncogenic
disorder involving a receptor protein tyrosine kinase
polypeptide/adaptor polypeptide complex comprising:
 (a) exposing at least one compound to a
 peptide comprising a functional portion of a
10 member of the receptor protein tyrosine kinase
polypeptide/adaptor polypeptide complex for a
time sufficient to allow binding of the compound
to the functional portion of the member;
 (b) removing non-bound compounds; and
15 (c) detecting the presence of the compound
bound to the functional portion of the member of
the protein tyrosine kinase polypeptide/adaptor
polypeptide complex,
thereby identifying a compound to be tested for an
20 ability to modulate an oncogenic disorder involving a
protein tyrosine kinase polypeptide/adaptor
polypeptide complex.

2. The method of Claim 1 wherein the receptor
25 protein tyrosine kinase polypeptide of the receptor
protein tyrosine kinase polypeptide/adaptor
polypeptide complex is a HER2 polypeptide.

3. The method of Claim 1 wherein the adaptor
30 polypeptide of the receptor protein tyrosine kinase
polypeptide/adaptor polypeptide complex is a GRB
polypeptide.

35

4. The method of Claim 3 wherein the GRB polypeptide is a GRB-1, GRB-2, GRB-4, GRB-7, or GRB-10 polypeptide.

5 5. The method of Claim 1 wherein the receptor protein tyrosine kinase polypeptide of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a HER2 polypeptide and the adaptor polypeptide of the protein tyrosine kinase
10 polypeptide/adaptor polypeptide complex is a GRB-7 polypeptide so that the protein tyrosine kinase polypeptide/adaptor polypeptide complex is a HER2 polypeptide/GRB-7 adaptor polypeptide complex.

15 6. The method of Claim 1 wherein the peptide comprising a functional portion of a member of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex comprises a peptide having at least 1 phosphorylated tyrosine amino acid residue.

20

7. The method of Claim 1 wherein the peptide comprising a functional portion of a member of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex comprises a functional portion of
25 a phosphorylation domain.

8. The method of Claim 1 wherein the peptide comprising a functional portion of a member of the receptor protein tyrosine kinase polypeptide/adaptor
30 polypeptide complex comprises a functional portion of an SH2 domain, and SH3 domain, an SH2-binding domain, or an SH3-binding domain.

35

9. The method of Claim 8 wherein the functional portion of the SH2-binding or the SH3-binding domain is at least 4 amino acid residues in length.

5 10. The method of Claim 8 wherein the functional portion of the SH3-binding domain is at least 10 amino acid residues in length.

10 11. The method of Claim 1 wherein the peptide comprising a functional portion of a member of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex comprises a receptor protein tyrosine kinase extracellular domain peptide.

15 12. The method of Claim 11 wherein the receptor protein tyrosine kinase polypeptide extracellular domain peptide is capable of binding a ligand of the receptor protein tyrosine kinase polypeptide.

20 13. The method of Claim 1 wherein the oncogenic disorder is a human breast cancer.

25 14. A method for identifying a compound to be tested for an ability to modulate an oncogenic disorder involving a receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex comprising: exposing at least compound to a receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex for a time sufficient to allow disruption of
30 the complex, and detecting the disruption of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex, so that if disruption of the complex has occurred, a compound to be tested for an ability to modulate an oncogenic disorder involving a

35

protein tyrosine kinase polypeptide/adaptor
polypeptide complex is identified.

15. The method of Claim 14 wherein the
5 disruption of the receptor protein tyrosine kinase
polypeptide/adaptor polypeptide complex is a
separation of the receptor protein tyrosine kinase
polypeptide/adaptor polypeptide complex components or
a decrease in the activity of the receptor protein
10 tyrosine kinase polypeptide/adaptor polypeptide
complex.

16. The method of Claim 14 wherein the receptor
protein tyrosine kinase polypeptide of the protein
15 tyrosine kinase polypeptide/adaptor polypeptide
complex is a HER2 polypeptide.

17. The method of Claim 14 wherein the adaptor
polypeptide of the receptor protein tyrosine kinase
20 polypeptide/adaptor polypeptide complex is a GRB
polypeptide.

18. The method of Claim 17 wherein the GRB
polypeptide is a GRB-1, GRB-2, GRB-4, GRB-7, or GRB-10
25 polypeptide.

19. The method of Claim 14 wherein the receptor
protein tyrosine kinase polypeptide of the receptor
protein tyrosine kinase polypeptide/adaptor
30 polypeptide complex is a HER2 polypeptide and the
adaptor polypeptide of the receptor protein tyrosine
kinase polypeptide/adaptor polypeptide complex is a
GRB-7 polypeptide so that the receptor protein
tyrosine kinase polypeptide/adaptor polypeptide
35

complex is a HER2 polypeptide/GRB-7 adaptor polypeptide complex.

20. The method of Claim 14 wherein the oncogenic
5 disorder is a human breast cancer.

21. A method for identifying a compound to be tested for an ability to modulate an oncogenic disorder involving a receptor protein tyrosine kinase
10 polypeptide/adaptor polypeptide complex comprising:

- (a) contacting the compound to a cell capable of forming a receptor tyrosine kinase polypeptide/adaptor polypeptide complex for a time sufficient to allow binding of the compound
15 to the receptor protein tyrosine kinase polypeptide of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex;
- (b) detecting the level of receptor protein tyrosine kinase polypeptide/adaptor polypeptide
20 complex present in the cell of step (a);
- (c) detecting the level of receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex present in a cell of the type in step (a) that has not contacted the compound; and
- 25 (d) comparing the level of receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex detected in step (b) to the level detected in step (c), so that if the level detected in step (c) is greater than the level
30 detected in step (b), a compound to be tested for an ability to modulate an oncogenic disorder involving a receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is identified.

35

22. The method of Claim 21 wherein the level of receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is the amount of receptor protein tyrosine kinase polypeptide/adaptor polypeptide
5 complex present in the cell, or is the activity of the receptor protein tyrosine kinase polypeptide/adaptor complex present in the cell.

23. The method of Claim 21 wherein the receptor
10 protein tyrosine kinase polypeptide is a HER2 polypeptide.

24. The method of Claim 21 wherein the adaptor polypeptide of the receptor protein tyrosine kinase
15 polypeptide/adaptor polypeptide complex is a GRB polypeptide.

25. The method of Claim 24 wherein the GRB
20 polypeptide is a GRB-1, GRB-2, GRB-4, GRB-7, or GRB-10 polypeptide.

26. The method of Claim 21 wherein the oncogenic disorder is a human breast cancer.
25

27. A method for identifying a compound capable of modulating the transformation capability of a receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex comprising:
30 (a) exposing at least one compound to a cell capable of forming the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex, in which the formation of the complex leads to the cell's transformation, for a time sufficient to disrupt or
35 inhibit the formation of the complex; and

(b) measuring the transformation state of the cell;
so that if transformation of the cell is reversed or inhibited, a compound is identified that modulates the transformation capability of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex.

28. The method of Claim 27 wherein the receptor protein tyrosine kinase polypeptide is a HER2 polypeptide.

29. The method of Claim 27 wherein the adaptor polypeptide of the receptor protein tyrosine kinase/adaptor polypeptide complex is a GRB polypeptide.

30. The method of Claim 29 wherein the GRB polypeptide is a GRB-1, GRB-2, GRB-4, GRB-7, or GRB-10 polypeptide.

31. The method of Claim 27 wherein the oncogenic disorder is a human breast cancer.

32. A method of modulating an oncogenic disorder involving a receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex comprising, contacting a cell capable of forming the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex with an amount of a compound sufficient to disrupt the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complexes of the cell so that the oncogenic disorder is modulated.

35

33. The method of Claim 32 wherein the receptor protein tyrosine kinase polypeptide is a HER2 polypeptide.

5 34. The method of Claim 32 wherein the adaptor polypeptide of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a GRB polypeptide.

10 35. The method of Claim 34 wherein the GRB polypeptide is a GRB-1, GRB-2, GRB-4, GRB-7, or GRB-10 polypeptide.

15 36. The method of Claim 32 wherein the receptor protein tyrosine kinase polypeptide of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a HER2 polypeptide and the adaptor polypeptide of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a
20 GRB-7 polypeptide so that the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a HER2 polypeptide/GRB-7 adaptor polypeptide complex.

25 37. The method of Claim 32 wherein the oncogenic disorder modulated is a human breast cancer.

30 38. A method of modulating an oncogenic disorder involving a receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex in a mammal comprising, administering to the mammal an amount of a compound sufficient to disrupt the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex so that the oncogenic disorder is modulated.

35

39. The method of Claim 38 wherein the receptor protein tyrosine kinase polypeptide of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a HER2 polypeptide.

5

40. The method of Claim 38 wherein the adaptor polypeptide of the protein tyrosine kinase polypeptide/adaptor polypeptide complex is a GRB polypeptide.

10

41. The method of Claim 40 wherein the GRB polypeptide is a GRB-1, GRB-2, GRB-4, GRB-7, or GRB-10 polypeptide.

15

42. The method of Claim 38 wherein the receptor protein tyrosine kinase polypeptide of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a HER2 polypeptide and the adaptor polypeptide of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a GRB-7 polypeptide so that the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a HER2 polypeptide/GRB-7 adaptor polypeptide complex.

20

43. The method of Claim 38 wherein the oncogenic disorder modulated is a human breast cancer.

44. A method for prognostic evaluation of a patient suspected of exhibiting an oncogenic disorder involving a receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex comprising:

(a) determining the concentration of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex or the concentration of the

35

receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex component present in a biological sample, taken from the patient, suspected of containing oncogenic tissue; and

- 5 (b) comparing the level determined in step (a) to the concentration range of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex, or the concentration of the receptor protein tyrosine kinase polypeptide known to be present in
10 normal, non-oncogenic tissue of the same type as present in the biological sample.

45. The method of Claim 44 wherein the oncogenic disorder is a human breast cancer.

15

46. The method of Claim 44 wherein the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a HER2 polypeptide/GRB-7 polypeptide complex.

20

47. A method for prognostic evaluation of a patient suspected of exhibiting an oncogenic disorder involving a receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex comprising:

- 25 (a) determining the concentration of a component of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex present in a biological sample, taken from the patient, suspected of containing oncogenic tissue; and

- 30 (b) comparing the level determined in step (a) to the concentration range of the component of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex known to be present in normal, non-oncogenic tissue of the same type as present in
35 the biological sample.

48. The method of Claim 47 wherein the component of the receptor protein tyrosine kinase polypeptide/adaptor polypeptide complex is a protein tyrosine kinase polypeptide or an adaptor polypeptide.

5

49. The method of Claim 48 wherein the receptor protein tyrosine kinase polypeptide is a HER2 polypeptide.

10 50. The method of Claim 48 wherein the adaptor protein polypeptide is a GRB-7 polypeptide.

15

20

25

30

35